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Carbon radical addition to *N*-sulfonylimines mediated by triethylborane or zinc

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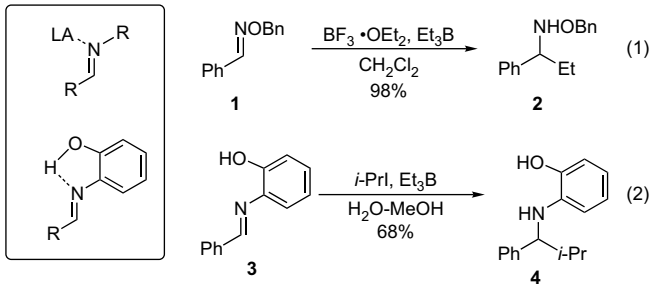
ABSTRACT

The utility of *N*-sulfonylimines as radical acceptors was investigated under the different reaction conditions such as the stannyl radical-mediated addition reaction, the triethylborane-mediated tin-free radical reaction, and the zinc-mediated aqueous-medium radical reaction. The alkyl radical addition reaction of *N*-sulfonylimines proceeded effectively without the activation by Lewis acid. These reactions were successfully extended to one-pot reactions for preparing a wide range of amine derivatives.

1. Introduction

The carbon–nitrogen double bond has attracted significant attention as an excellent radical acceptor, and thus numerous useful intramolecular carbon–carbon bond-forming reactions of imine derivatives are available.[1,2] However, until recently, the intermolecular radical addition to imine derivatives has not been widely studied. Therefore, the screening of reactive imino acceptors has been a challenging task in synthetic organic chemistry.[1c,3–10] In general, the efficient intermolecular radical addition to imine derivatives required some activation for lowering LUMO energy of C=N bond, which classified two types of method. The Lewis or Brønsted acids were employed for increasing the reactivity of imine derivatives toward nucleophilic carbon radical by coordination at nitrogen atom of C=N bond. We previously reported that an alkyl radical addition to benzaldehyde oxime ether **1** proceeded smoothly by using $BF_3 \cdot OEt_2$ as Lewis acid, to give the desired adducts in high yields.[11] In the case of unactivated oxime ethers, the addition of Lewis acid was found to be essential for the successful reaction (Eq. 1). Aldimine **3** bearing the phenolic hydroxyl group, which acted as Brønsted acid by intramolecular hydrogen bonding interaction, exhibited good reactivity on the radical addition reaction even in aqueous media (Eq. 2).[12] As a direct modification of substrates, the introduction of an electron-withdrawing group such as the carbonyl or sulfonyl group[5] at iminoic carbon enhances the reactivity of C=N bond. We reported that the triethylborane-induced radical addition to oxime ether **5** activated by an electron-withdrawing methoxycarbonyl group proceeded smoothly even in the absence of any Lewis acid to give the excellent yield of adduct **6** (Eq. 3).[9a,b,13] However, this method strictly limited the structure of substrate, although it was the useful tool for the synthesis of α-amino acids. Therefore, we focused our attention to introduce the activating substituent on nitrogen atom of C=N bond, from the point of view in synthetic application. *N*-Sulfonylimines are well known to be as good substrates for the nucleophilic addition of organometallic reagents.[14] Therefore, the electron deficient imines bearing an *N*-sulfonyl group are expected to exhibit the high reactivity toward nucleophilic alkyl radicals (Eq. 4). Our recent studies show that *N*-sulfonylimines act as excellent radical acceptors.[15] From a practical point of view, it is worth noting that the radical reaction of *N*-sulfonylimines does not require highly purified reagents or solvent and proceeds effectively even in the absence of Lewis acid. More recently, the viability of *N*-sulfonylimines was also demonstrated in the dialkylzinc-induced radical reactions by Tomioka's group.[8d–f,16,17] In this paper, we present a full study of the radical reaction of *N*-sulfonylimines using Et_3B as a radical initiator. We also report the one-pot reaction and zinc-mediated reaction in aqueous media.

1) activation by coordination of Lewis acid or Brønsted acid



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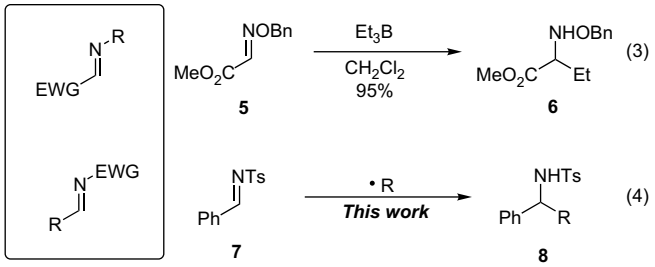
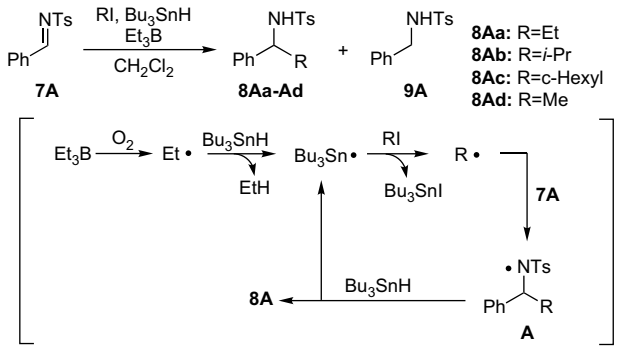
2) activation by latent electron-withdrawing group



2. Results and discussion

2.1. Triethylborane-induced radical reaction using Bu_3SnH

In order to test the reactivity of *N*-sulfonylimines toward nucleophilic alkyl radical, we initially examined the ethyl radical addition to **7A** using Et_3B as an ethyl radial source (Scheme 1). When the reaction was carried out at 25 °C in the presence of Bu_3SnH (2.5 equiv), the desired product **8Aa** was not obtained, but the reduction of C=N bond exclusively occurred to give amine **9A** (Table 1, entry 1). We recently studied the Bu_3SnH-promoted reduction of the carbon–nitrogen double bond of imine derivatives.[18] Based on this result, the radical addition reaction of **7A** was next performed



Scheme 1. Stannyl radical-mediated radical addition to **7A**.

at −78 °C, to suppress the tin hydride-mediated reduction. As expected, the desired adduct **8Aa** was predominately obtained in 45% yield accompanied with a trace amount of amine **9A** (entry 2). This result indicates that *N*-sulfonylimine displays an excellent reactivity in the intermolecular radical reaction in the absence of Lewis acid even at −78 °C.

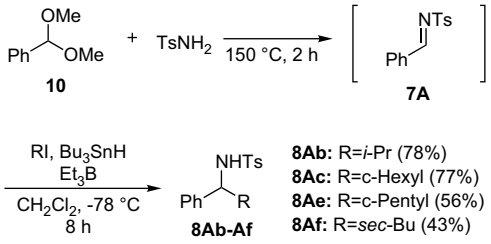
Good chemical yields were observed in the radical addition reaction using secondary alkyl radical precursors such as isopropyl and cyclohexyl iodides (entries 3 and 4), although no methylated product **8Ad** was obtained in the reaction with methyl iodide because the generation process of primary radical is less effective (entry 5). The reaction would be initiated by the generation of alkyl radical from alkyl iodide and stannyl radical. The alkyl radical attacked *N*-sulfonylimine **7A** to generate aminyl radical **A** stabilized by an electron-withdrawing sulfonyl group. The aminyl radical **A** was reduced with Bu_3SnH to furnish **9A** and regenerate stannyl radical into propagating cycle.

Table 1
Stannyl radical-mediated radical addition to **7A**

Entry	RI	*T* (°C)	Time (h)	Yield (%)	
				8Aa–Ad	**9A**
1[a]	None	25	4	Trace	50
2[a]	None	−78	8	45	Trace
3[b]	*i*-PrI	−78	8	85	Trace
4[b]	*c*-Hexyl I	−78	8	82	Trace
5[b]	MeI	−78	8	n.d.[c]	Trace

[a] Reactions were carried out with Et_3B (5 equiv) and Bu_3SnH (2.5 equiv).
[b] Reactions were carried out with RI (5 equiv), Et_3B (2.5 equiv), and Bu_3SnH (2.5 equiv).
[c] Complex mixture of unknown products was obtained.

The development of one-pot reactions has provided the rapid means for the preparation of complex molecules. Moreover, the attraction to the synthetic chemists lies in the multitude of advantages that include higher yields than almost any sequential synthesis and a single purification step. The present radical addition reaction was successfully extended to one-pot reaction involving the formation of *N*-sulfonylimine (Scheme 2). Benzaldehyde dimethylacetal **10** was used instead of benzaldehyde. Condensation of dimethylacetal **10** with *p*-toluenesulfonamide at 150 °C proceeded smoothly without any additives under the solvent-free conditions to give the *N*-tosylimine **7A** as a solid. After CH_2Cl_2 was added to the same reaction vessel to dissolve **7A**, RI, Bu_3SnH, and Et_3B were subsequently added at −78 °C and then the reaction mixture was stirred for 8 h. When the reaction was carried out with *i*-PrI, the isopropylated product **8Ab** was obtained in 78% yield after the purification. The other radical precursors such as cyclohexyl, cyclopentyl, and *sec*-butyl iodides also worked well to give **8Ac**, **8Ae**, and **8Af** in good yields.

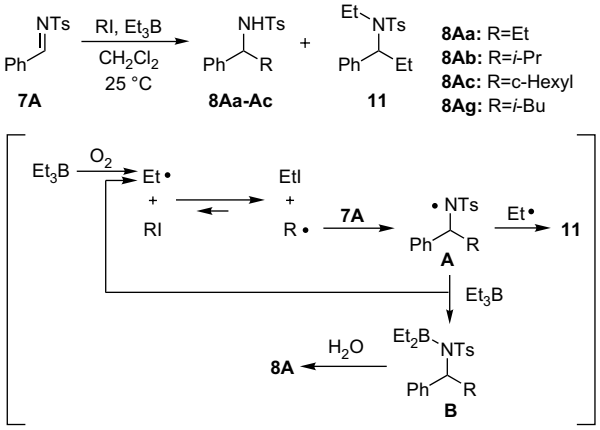


Scheme 2. One-pot reaction of imine formation and radical reaction.

2.2. Tin-free radical reaction

Free radical reaction largely relied on toxic organotin chemistry. Therefore, we have studied the tin-free radical reactions including atom-transfer processes or single-electron transfer (SET) processes. Based on our recent results,[3b] we next examined the reaction of *N*-sulfonylimine **7A** in the absence of Bu_3SnH (Scheme 3).

In the absence of Bu_3SnH, the reaction of **7A** with an ethyl radical was run in dichloromethane at 25 °C by using Et_3B (Table 2,



Scheme 3. Et_3B-mediated tin-free radical addition to **7A**.

Table 2
Tin-free radical addition to **7A**

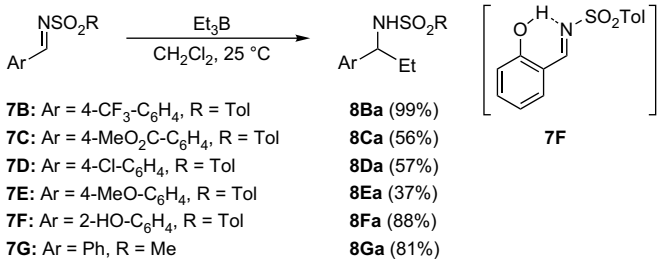
Entry	RI	Time (h)	Product	Yield (%)
1[a]	None	2	**8Aa**	84[b]
2[c]	*i*-PrI	3	**8Ab**	80
3[c]	*c*-Hexyl I	3	**8Ac**	55
4[c]	*i*-BuI	7	**8Ae**	n.d.[d]

[a] Reaction was carried out with Et_3B (5 equiv×3).
[b] Diethylated product **11** (12% yield) was obtained.
[c] Reactions were carried out with RI (30 equiv) and Et_3B (5 equiv×3).
[d] Adduct **8Aa** was obtained in 58% yield.

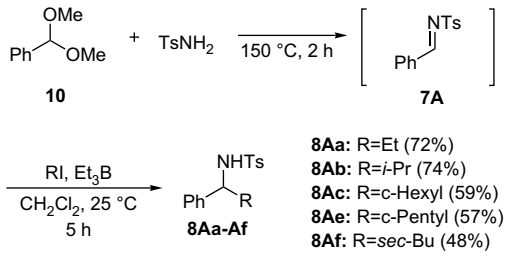
entry 1). The desired adduct **8Aa** was obtained in 84% yield, accompanied with 12% yield of the *C*,*N*-diethylated product **11**, although the large amount of Et_3B (5 equiv×3) was required to complete the reaction. Good chemical yield was also observed in the reaction with isopropyl radical (entry 2). Moreover, the reaction with more nucleophilic secondary isopropyl radical gave selectively adduct **8Ab** with no formation of the *C*,*N*-dialkylated products. A slightly decrease in yield was observed in the reaction with cyclohexyl radical, possibly due to the bulkiness of intermediate radical **A**, which prevented Et_3B to trap radical **A** (entry 3). The reaction with unstable primary alkyl radical such as isobutyl radical did not give the desired product, but significant amount of ethylated product **8Aa** was obtained because of inefficient iodine atom-transfer process (entry 4). The present triethylborane-mediated tin-free radical reaction has a tremendous practical advantage over the stannyl radical-mediated reaction involving the troublesome work-up to remove the tin residues from reaction mixture. In the tin-free reaction conditions, Et_3B played multiple role concerning reaction pathway; thus, it acted as not only a radical initiator but also a radical terminator to trap the intermediate radical **A** to give an adduct **B** and a chain-propagating ethyl radical.

To demonstrate the scope of the tin-free radical reaction, we subjected a series of *N*-sulfonylimines **7B**–**G** to the ethyl radical addition reaction (Scheme 4). The radical reaction of **7B** possessing a strong electron-withdrawing CF_3 group proceeded smoothly to give adduct **8Ba** in 99% yield, although the reaction of **7E** with an electron-donating substituent gave the lower yield of product **8Ea**. It is noteworthy to mention that *N*-sulfonylimine **7F** having phenolic hydroxy group has the high reactivity, probably due to the activation and stability by the intramolecular hydrogen-bond between a C=N bond and a phenolic 2-hydroxy group. The radical addition to **7F** proceeded effectively within 2 h only with 5 equiv of Et_3B to give the desired product **8Fa** in 88% yield. The mesyl group was also able to activate imine moiety for radical addition reaction as shown in the reaction of **7G**.

The tin-free radical reaction could be extended to the one-pot reaction, which proceeded efficiently furnishing moderate to high yields of desired amines (Scheme 5). The second step of tin-free one-pot reaction was able to be carried out at room temperature. Thus, the tin-free radical reaction is more practical than the stannyl radical-mediated reaction conducted at −78 °C.



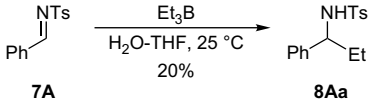
Scheme 4. Ethyl radical addition to **7B**–**7G**.



Scheme 5. One-pot reaction of imine formation and tin-free radical.

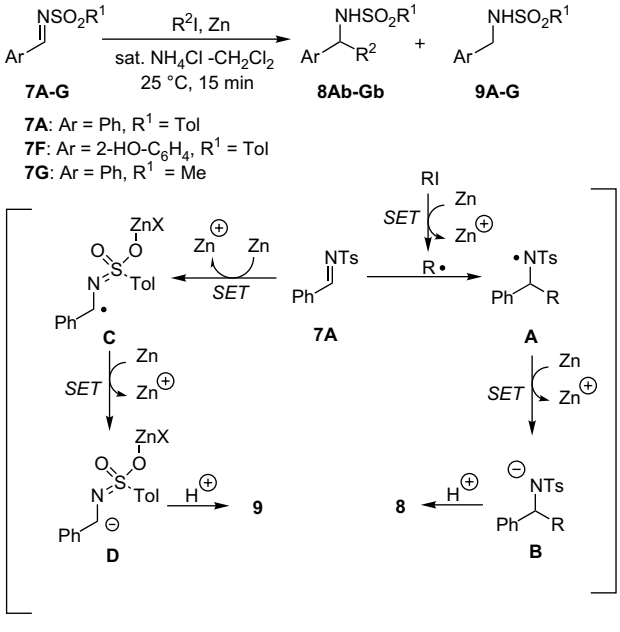
2.3. Zinc-induced reaction in aqueous media

Today's environmental concerns encourage the development of greener reaction conditions. The use of water as a solvent has received considerable attention from economic and environmental points of view in synthetic organic chemistry.[19] Particularly, carbon–carbon bond-formation reaction in aqueous media is a challenging task.[20] We have recently demonstrated that the radical reactions of imines such as oxime ethers, hydrazones, and nitrones can be performed in aqueous media by using Et_3B.[21] In our preliminary study, the Et_3B-induced ethyl radical addition reaction of **7A** in aqueous media was investigated. However, the formation of desired product **8Aa** in good yield was difficult due to the competitive hydrolysis of C=N bond giving $TsNH_2$ (Scheme 6).



Scheme 6. Et_3B-mediated ethyl radical addition to **7A** in aqueous media.

In an attempt to further improve the yield of products in the tin-free aqueous-medium reaction, the reaction was examined under the metal-mediated single-electron transfer reaction conditions.[22,23] Metallic zinc was used as a single-electron transfer radical initiator (Scheme 7). To micro tube containing **7A**, *i*-PrI, zinc, and dicholoromethane as a cosolvent was added dropwise saturated NH_4Cl over 15 min at 25 °C (Table 3, entry 1).



Scheme 7. Zinc-mediated alkyl radical addition to **7A**, **7F**, and **7G**.

Table 3
Zinc-mediated alkyl radical addition to **7A**, **7F**, and **7G**[a]

Entry	Ar	R^1	R^2	Product	Yield (%)	
					8	**9A**, **9F**, **9G**
1	Ph	Tol	*i*-Pr	**8Ab**	73	8
2[b]	Ph	Tol	*i*-Pr	**8Ab**	No reaction	
3	Ph	Tol	*c*-Hexyl	**8Ac**	71	12
4	Ph	Tol	*c*-Pentyl	**8Ae**	64	18
5	Ph	Tol	*sec*-Bu	**8Af**	56	10
6	Ph	Tol	*tert*-Bu	**8Ah**	66	20
7	Ph	Tol	Me	**8Ad**	n.d.	16
8	2-OH–C_6H_4	Tol	*i*-Pr	**8Fb**	64	8
9[c]	Ph	Me	*i*-Pr	**8Gb**	21	37

[a] Reactions were carried out with Zn (7 equiv), RI (5 equiv), and satd NH_4Cl in CH_2Cl_2.
[b] Reaction was carried out in the presence of galvinoxyl free radical (5 equiv).
[c] A small amount of $MeSO_2NH_2$ was obtained.

The isopropylated product **8Ab** was obtained in 73% yield, along with the reduced product **9A** as a result of the zinc-induced reduction of C=N bond. The reaction did not take place in the presence of galvinoxyl free radical as a radical scavenger (entry 2). It suggests that the zinc-induced reaction proceeded via radical pathway as indicated in Scheme 7. Isopropyl radical, generated from isopropyl iodide with zinc via single-electron transfer, attacked the sulfonylimine **7A** to form aminyl radical **A**, which was reduced by zinc and then protonated to afford the desired product **8Ab**. On the other hand, amine **9A** was obtained via direct single-electron transfer reduction of **7A** by zinc. Not only secondary alkyl radicals but also the bulky *tert*-butyl radical worked well under similar reaction conditions (entries 3–6), although methyl radical was not efficient (entry 7). The isopropyl radical addition to *N*-sulfonylimine **7F** carrying phenolic hydroxy group also proceeded (entry 8). However, unstable *N*-methylsulfonylimine **7G** gave a low yield of product **8Gb**, due to the competitive reduction and hydrolysis (entry 9). It appears that the formation of **9** depended on the reactivity of *N*-sulfonylimines with alkyl radicals. Thus, the reaction with bulky *tert*-butyl radical and the reaction of reactive *N*-mesylimine **7G** led to significant amount of reduced product **9** (entries 6 and 9). In our previous studies on indium-mediated radical reaction in aqueous media, the alkyl radical addition to *N*-sulfonylimine proceeded relatively slow in which the substrate underwent hydrolysis as a significant side reaction. In contrast, it should be noted that the present zinc-mediated reaction completed within 15 min thus being able to suppress the side reaction such as a hydrolysis.

3. Conclusion

For the first time, we have demonstrated the utility of *N*-sulfonylimines as radical acceptors under three reaction conditions. The triethylborane-induced reaction was successfully extended to one-pot reaction for preparing a wide range of amine derivatives. The known examples of zinc-mediated carbon–carbon bond-forming reactions in the aqueous media are mainly limited to allylations of carbonyl compounds or imines; thus, it is noteworthy that the present radical reaction is useful for general alkylation of imines.

4. Experimental

4.1. General

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 200, 300, or 500 MHz and at 50 or 125 MHz, respectively. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by EI or CI methods. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$). Flash column chromatography was performed using E. Merck Kieselgel 60 (230–400 mesh). The physical and spectroscopic data of **8Aa**,[24] **8Ab**,[25] **8Ac**,[8b] **8Ba**,[24] **8Da**,[24] **8Ea**,[24] **8Ga**,[24] **9A**,[26] **9F**,[27] and **9G**[28] are in consistent with those reported in the literature.

4.2. Triethylborane-induced radical reaction using Bu_3SnH

*4.2.1. Stannyl radical-mediated ethyl radical addition to **7A** at 25 °C (Table 1, entry 1)*

To a solution of **7A** (50 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) were added Bu_3SnH (0.13 mL, 0.48 mmol) and Et_3B (1.0 M in hexane, 0.97 mL, 0.97 mmol) under N_2 atmosphere at 25 °C. After being stirred at the same temperature for 4 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt, 2:1) afforded impure **7A**, which was re-purified by preparative TLC (hexane/AcOEt, 4:1) to give pure **9A**[26] (25 mg, 50%).

*4.2.2. Stannyl radical-mediated ethyl radical addition to **7A** at −78 °C (Table 1, entry 2)*

To a solution of **7A** (50 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) were added Bu_3SnH (0.13 mL, 0.48 mmol) and Et_3B (1.0 M in hexane, 0.97 mL, 0.97 mmol) under N_2 atmosphere at −78 °C. After being stirred at the same temperature for 8 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt, 2:1) afforded impure **8Aa**, which was re-purified by preparative TLC (hexane/AcOEt, 4:1) to give pure **8Aa**[24] (25 mg, 45%).

*4.2.3. Stannyl radical-mediated alkyl radical addition to **7A** at −78 °C (Table 1, entries 3–5)*

To a solution of **7A** (50 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) were added RI (0.97 mmol), Bu_3SnH (0.13 mL, 0.48 mmol), and Et_3B (1.0 M in hexane, 0.48 mL, 0.48 mmol) under N_2 atmosphere at −78 °C. After being stirred at the same temperature for 8 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt, 2:1) afforded impure **8Ab**–**8Ac**, which were re-purified by preparative TLC (hexane/AcOEt, 4:1) to give pure **8Ab**[25]–**8Ac**.[8b]

4.2.4. One-pot reaction for the imine formation and stannyl radical-mediated radical addition reaction

A mixture of benzaldehyde dimethylacetal **10** (53 mg, 0.35 mmol) and *p*-$TsNH_2$ (50 mg, 0.29 mmol) was stirred at 150 °C for 2 h and then it was cooled to room temperature to give **7A**, which was dissolved in CH_2Cl_2 (15 mL). RI (0.97 mmol), Bu_3SnH (0.13 mL, 0.48 mmol), and Et_3B (1.0 M in hexane, 0.48 mL, 0.48 mmol) were consecutively added to the solution of **7A** under N_2 atmosphere at −78 °C. After being stirred at the same temperature for 8 h, the reaction mixture was diluted with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt, 2:1) afforded impure **8Ab**–**8Af**, which were re-purified by preparative TLC (hexane/AcOEt, 4:1) to give pure **8Ab**–**8Af**.

*4.2.5. N-Cyclopentyl(phenyl)methyl-4-methylbenzenesulfonamide (**8Ae**)*

Colorless crystals. Mp 139–141 °C (AcOEt/hexane). IR ($CHCl_3$) 3261, 1322, 1164 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.48–7.44 (2H, m),

7.10–6.92 (7H, m), 5.20–5.39 (1H, m), 4.02 (1H, dd, J=9.0, 8.0 Hz), 2.31 (3H, s), 2.24–2.03 (1H, m), 1.92–1.75 (1H, m), 1.65–0.95 (7H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.5, 140.9, 137.7, 129.0, 128.0, 126.9, 126.85, 126.78, 63.01, 46.6, 29.9, 25.02, 24.97, 21.3. HRMS calcd for $C_{19}H_{23}NO_2S$ (M^+) 329.1449, found 329.1429. Anal. Calcd for $C_{19}H_{23}NO_2S$: C, 69.27; H, 7.04; N, 4.25. Found: C, 69.27; H, 7.13; N, 4.24.

4.2.6. 4-Methyl-N-(2-methyl-1-phenylbutyl)benzenesulfonamide (**8Af**)

White solid (a 1:1 mixture of diastereomers). IR ($CHCl_3$) 3272, 1321, 1165 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53–7.46 (2H, m), 7.10–6.90 (7H, m), 5.50 (1H, m), 4.19 (1/2H, dd, J=8.6, 6.6 Hz), 4.10 (1/2H, t, J=8.0 Hz), 2.31 (3H, s), 1.74–1.57 (2H, m), 1.26–0.65 (7H, m); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.6, 142.5, 140.1, 139.6, 137.54, 137.49, 129.0, 127.8, 126.9, 126.9, 126.7, 126.6, 62.6, 62.1, 41.0, 40.6, 25.8, 25.1, 21.2, 15.4, 14.6, 11.2, 11.0. HRMS calcd for $C_{18}H_{23}NO_2S$ (M^+) 317.1448, found 317.1457.

4.3. Tin-free radical reaction

4.3.1. Et_3B-induced tin-free ethyl radical addition to **8A** (Table 2, entry 1)

To a solution of **7A** (50 mg, 0.19 mmol) in CH_2Cl_2 (5 mL) was added Et_3B (1.0 M in hexane, 0.95 mL, 0.95 mmol) three times in every 1 h under N_2 atmosphere at 25 °C. After being further stirred at the same temperature for 15 min, the reaction mixture was diluted with satd $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt, 5:1) afforded **8Aa** (46 mg, 84%) and **11** (7.2 mg, 12%).

4.3.2. N-Ethyl-4-methyl-N-(1-phenylpropyl)benzenesulfonamide (**11**)

Colorless oil. IR ($CHCl_3$) 2973, 2932, 1715, 1335, 1159 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (2H, d, J=8.5 Hz), 7.29–7.20 (7H, m), 4.89 (1H, dd, J=9.0, 7.0 Hz), 3.18–3.06 (2H, m), 2.42 (3H, s), 2.10–2.01 (1H, m), 1.82–1.74 (1H, m), 0.93 (1H, t, J=7.0 Hz), 0.87 (1H, t, J=7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.8, 138.8, 129.5, 128.4, 128.3, 127.7, 127.0, 62.2, 39.0, 24.8. HRMS calcd for $C_{18}H_{23}NO_2S$ (M^+) 317.1448, found 317.1452.

4.3.3. Et_3B-induced tin-free alkyl addition to **7A** (Table 2, entries 2 and 3)

To a solution of **7A** (50 mg, 0.19 mmol) and RI (5.7 mmol) in CH_2Cl_2 (5 mL) was added Et_3B (1.0 M in hexane, 0.95 mL, 0.95 mmol) three times in every 2 h under N_2 atmosphere at 25 °C. After being further stirred at the same temperature for 1 h, the reaction mixture was diluted with satd $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt, 5:1) afforded **8Ab**–**8Ac**.

4.3.4. Et_3B-induced tin-free ethyl radical addition to **7B**–**7E** and **7G**

To a solution of **7B**–**7G** (50 mg) in CH_2Cl_2 (5 mL) was added Et_3B (1.0 M in hexane, 5 equiv) three times in every 1 h under N_2 atmosphere at 25 °C. After being further stirred at the same temperature overnight, the reaction mixture was diluted with satd $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt, 3:1) afforded **8Ba**–**8Ea**, and **8Ga**.[24]

4.3.5. 4-(1-{[(4-Methylphenyl)sulfonyl]amino}propyl)benzoic acid methyl ester (**8Ca**)

Colorless crystals. Mp 132–133.5 °C (AcOEt/hexane). IR ($CHCl_3$) 3266, 1721, 1286, 1160 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.43 (2H, d, J=8.4 Hz), 7.55 (2H, d, J=8.4 Hz), 7.16–7.05 (4H, m), 5.96–5.86 (1H, m), 4.25 (1H, q, J=7.2 Hz), 3.89 (3H, s), 2.33 (3H, s), 1.86–1.62 (2H, m), 0.78 (3H, t, J=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.7, 146.0, 143.0, 137.5, 129.5, 129.2, 128.9, 126.9, 126.6, 59.4, 52.0, 30.3, 21.2, 10.3. HRMS calcd for $C_{18}H_{22}NO_4S$ (M^++H) 348.1268, found 348.1265. Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.23; H, 6.09; N, 4.03. Found: C, 62.19; H, 6.14; N, 3.98.

4.3.6. N-[1-(2-Hydroxyphenyl)propyl]-4-methylbenzenesulfonamide (**8Fa**)

To a solution of **7F** (50 mg, 0.18 mmol) in CH_2Cl_2 (5 mL) was added Et_3B (1.0 M in hexane, 5 equiv) under N_2 atmosphere at 25 °C. After being stirred at the same temperature for 2 h, the reaction mixture was diluted with satd $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt, 3:1) afforded **8Fa** (45 mg, 84%) as colorless crystals. Mp 116–118 °C (AcOEt/hexane). IR ($CHCl_3$) 3453, 3260, 1455, 1316, 1159 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53 (2H, d, J=8.2 Hz), 7.07–6.52 (6H, m), 5.91 (1H, br s), 5.62 (1H, br d, J=9.0 Hz), 4.21 (1H, m), 2.31 (3H, s), 1.91–1.74 (2H, m), 0.82 (3H, t, J=8.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.0, 143.0, 137.0, 129.1, 129.0, 128.3, 126.0, 120.2, 116.1, 59.1, 28.7, 21.4, 11.0. HRMS calcd for $C_{16}H_{19}NO_3S$ (M^++H) 305.1085, found 305.1080. Anal. Calcd for $C_{18}H_{21}NO_4S$: C, 62.93; H, 6.27; N, 4.59. Found: C, 62.67; H, 6.32; N, 4.50.

4.3.7. One-pot reaction for the imine formation and tin-free radical addition reaction

A mixture of benzaldehyde dimethylacetal **10** (213 mg, 1.40 mmol) and p-$TsNH_2$ (200 mg, 1.17 mmol) was stirred at 150 °C for 2 h and then it was cooled to room temperature to give **7A**, which was dissolved in CH_2Cl_2 (10 mL). RI (5.7 mmol) and Et_3B (1.0 M in hexane, 0.95 mL, 0.95 mmol) were consecutively added to the solution of **7A** under N_2 atmosphere at 25 °C. After being stirred at the same temperature for 2 h, Et_3B (1.0 M in hexane, 0.95 mL, 0.95 mmol) was added two times in 2 h. After being further stirred at the same temperature for 1 h, the reaction mixture was diluted with satd $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by column chromatography on SiO_2 (hexane/AcOEt, 5:1) afforded **8Aa**–**8Af**.

4.3.8. Et_3B-induced tin-free ethyl radical addition to **7A** in H_2O–THF

To a solution of **7A** (50 mg, 0.19 mmol) in H_2O–THF (5:1, 5 mL) was added Et_3B (1.0 M in hexane, 0.95 mL, 0.95 mmol) three times in every 1 h under N_2 atmosphere at 25 °C. After being further stirred at the same temperature for 15 min, the reaction mixture was diluted with satd $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by preparative TLC (hexane/AcOEt, 5:1) afforded **8Aa** (11 mg, 20%).

4.4. Zinc-induced reaction in aqueous media

4.4.1. General procedure for zinc-meditated alkyl radical addition

To a micro tube containing N-sulfonylimine (50 mg), RI (5 equiv), zinc dust (7 equiv), and CH_2Cl_2 (0.1 mL) was added dropwise satd NH_4Cl (0.4 mL) at 25 °C over 15 min. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with satd NH_4Cl and then extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated at reduced pressure. Purification of the residue by preparative TLC (hexane/AcOEt, 3:1) afforded **8Ab**–**8Ah**, **8Fb**, or **8Gb** and **9A**, **9F**,[27] or **9G**.[28]

4.4.2. *N-(2,2-Dimethyl-1-phenylpropyl)-4-methylbenzenesulfonamide (**8Ah**)*

White solid. IR (neat) 3274, 2973, 1326, 1163 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.44–7.40 (2H, m), 7.06–6.90 (7H, m), 5.36–5.31 (1H, m), 4.03 (1H, m, J=9.2 Hz), 2.28 (3H, s), 0.89 (9H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 142.5, 138.2, 137.1, 128.9, 127.9, 127.4, 126.9, 126.6, 66.8, 35.1, 26.5, 21.2. HRMS calcd for $C_{18}H_{23}NO_2S$ (M^+) 317.1448, found 317.1446.

4.4.3. *N-[1-(2-Hydoroxyphenyl)-2-methylpropyl]-4-methylbenzenesulfonamide (**8Fb**)*

Colorless crystals. Mp 179–181 °C (AcOEt/hexane). IR (neat) 3465, 3285, 1599, 1312, 1163 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.47 (2H, d, J=8.2 Hz), 7.01–6.49 (6H, m), 5.70–5.56 (1H, m), 5.54–5.38 (1H, m), 3.92 (1H, t, J=8.8 Hz), 2.28 (3H, s), 2.20–2.03 (1H, m), 1.05 (3H, d, J=7.0 Hz), 0.68 (3H, d, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.5, 142.8, 130.0, 129.0, 128.1, 126.9, 125.8, 120.3, 115.9, 63.8, 32.7, 21.3, 20.0, 19.8. HRMS calcd for $C_{17}H_{21}NO_3S$ (M^+) 319.1241, found 319.1214. Anal. Calcd for $C_{17}H_{21}NO_3S$: C, 63.92; H, 6.63; N, 4.39. Found: C, 63.70; H, 6.55; N, 4.33.

4.4.4. *N-(2-Methyl-1-phenylpropyl)methanesulfonamide (**8Gb**)*

Colorless oil. IR (neat) 3022, 1602, 1331, 1152 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.40–7.24 (5H, m), 5.28–5.15 (1H, m), 4.16 (1H, t, J=8.2 Hz), 2.53 (3H, s), 2.06–1.88 (1H, m), 1.04 (3H, d, J=7.0 Hz), 0.83 (3H, d, J=7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 140.7, 128.5, 127.5, 127.5, 127.0, 64.1, 41.2, 34.2, 19.5, 19.0. HRMS calcd for $C_{11}H_{17}NO_2S$ (M^+) 227.0979, found 227.1001.

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